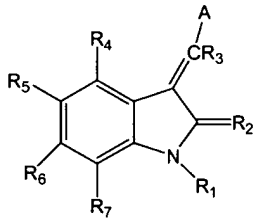
What is claimed is:

CLAIMS

1. A method of modulating abnormal cell proliferation, modulating the activity of VEGF, FGF, or PDGF on cells *in vivo* or *in vitro*, modulating tyrosine kinase signal transduction or treating or preventing an abnormal condition, said method comprising administering to a patient in need of such treatment a pharmaceutically acceptable composition comprising a therapeutically effective amount of one or more indolinone compounds of Formula I:



(I)

wherein,

R_1 is H or alkyl;

R_2 is O or S;

R_3 is H;

R_4, R_5, R_6, and R_7 are each independently selected from the group consisting of hydrogen alkyl, alkoxy, aryl, aryloxy, alkaryl, alkaryloxy, halogen, trihalomethyl, S(O)R, SO_2NRR', SO_3R, SR, NO_2, NRR', OH, CN, C(O)R, OC(O)R, NHC(O)R, $(CH_2)_nCO_2R$, CONRR', and $(CH_2)_nONRR'$;

A is selected from the group consisting of a 4,5,6,7-tetrahydroindole and a five-membered heteroaryl ring, wherein said five-membered ring is selected from the group consisting of thiophene, pyrrole, pyrazole, imidazole, 1,2,3-triazole, 1,2,4-triazole, oxazole, isoxazole, thiazole, isothiazole, 2-sulfonylfuran, 4-alkylfuran, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole, 1,2,3,4,-oxatriazole, 1,2,3,5-oxatriazole, 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole, 1,3,4-thiadaizole,

1,2,3,4-thiatriazole, 1,2,3,5-thiatriazole, and tetrazole, wherein said five-membered ring and said tetrahydroindole are optionally substituted with one or more substituents selected from the group consisting of alkyl, alkoxy, aryl, aryloxy, alkaryl, alkaryloxy, halogen, trihalomethyl, S(O)R, SO_2NRR', SO_3R, SR, NO_2, NRR', OH, CN, C(O)R, OC(O)R, NHC(O)R, $(CH_2)_nCO_2R$, CONRR', and $(CH_2)_nONRR'$;

n is 0-3;

R is selected from the group consisting of H, alkyl, and aryl; and

R' is selected from the group consisting of H, alkyl, and aryl, wherein said alkyl is optionally substituted with a six-membered heteroaliphatic ring, and wherein said six-membered ring is optionally substituted at one or more positions with substituents selected from the group consisting of alkyl, alkoxy, halogen, trihalomethyl, NO_2, and $(CH_2)_nCO_2R$.

2. The method of claim 1, wherein said A is selected from the group consisting of thiophene, pyrole, and 4,5,6,7-tetrahydroindole, optionally substituted with one or more substituents selected from the group consisting of alkyl, alkoxy, aryl, aryloxy, alkaryl, alkaryloxy, halogen, trihalomethyl, S(O)R, SO_2NRR', SO_3R, SR, NO_2, NRR', OH CN, C(O)R, OC(O)R, NHC(O)R, $(CH_2)_nCO_2R$, CONRR', and $(CH_2)_nONRR$.

3. The method of claim 1, wherein said indolinone compounds of Formula I are selected from the group consisting of Compound II, Compound III, Compound IV, Compound V, Compound VI, Compound VII, and Compound VIII.

4. The method of claim 1, wherein said composition further comprises one or more pharmaceutically acceptable excipients in a formulation.

5. The method of claim 4, wherein said formulation is at least one of parenteral, oral, or topical formulation.

6. The method of claim 1, wherein said effective amount comprises an amount in the range of from about 1 to about 1000 mg/m^2/day.

7. The method of claim 1, wherein said abnormal condition is endometriosis and/or arthritis.

8. A method of identifying one or more indolinone compounds of Formula I that inhibit growth factor-stimulated cell proliferation comprising the following steps:

(a) contacting cells with said one or more indolinone compounds;

(b) contacting said cells with one or more growth factors selected from the group consisting of VEGF, PDGF, and FGF; and

(c) monitoring an effect upon said cells.

9. The method of claim 8, wherein said cells are endothelial cells and are contacted with VEGF in step (b).

10. The method of claim 8, wherein said cells are smooth muscle cells and are contacted with PDGF in step (b).

11. The method of claim 8, wherein said cells are endothelial cells and are contacted with FGF in step (b).

12. A method of identifying one or more indolinone compounds of Formula I that are active in an adjuvant arthritis model in rats comprising the following steps:

(a) administering said one or more indolinone compounds to said rats; and

(b) monitoring an effect upon said rats.

13. The method of claim 12, wherein said one or more compounds are administered at a concentration in the range of from about 1 to about 1000 mg/m^2/day.

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14. A method modulating abnormal cell proliferation, modulating the activity of VEGF, FGF, or PDGF on cells *in vivo* or *in vitro* or modulating tyrosine kinase signal transduction, comprising administering to a patient in need of such treatment a pharmaceutically acceptable composition comprising a therapeutically effective amount of said one or more compounds identified by the method of either of claims 8 or 12, wherein said composition optionally includes one or more pharmaceutically acceptable excipients in at least one of parenteral, oral, or topical formulation.

15. A method of treating or preventing an abnormal condition by administering to a patient in need of such treatment a pharmaceutically acceptable composition comprising a therapeutically effective amount of said one or more compounds identified by the method of either of claims 8 or 12, wherein said abnormal condition is selected from the group consisting of arthritis, endometriosis, ocular neovascularization, solid tumor growth and metastases, and excessive scarring during wound healing, wherein said composition optionally includes one or more pharmaceutically acceptable excipients in at least one of parenteral, oral, or topical formulation.

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.Table 1: Summary of IC_{50} determination of test substances of HUVEC and inhibition of VEGF-stimulation by test substances without preincubation

group	Compound II in μM										
	control	400	80	16	3.2	0.64	0.128	0.0256	0.00512	0.0010	IC50 in μM
control	0.568	0.062	0.094	0.139	0.457	0.531	0.551	0.546	0.543	0.576	8.7
stand deviation +/-	0.017	0.005	0.004	0.009	0.027	0.017	0.011	0.004	0.023	0.015	
VEGF [10ng/m]	0.849	0.062	0.108	0.168	0.459	0.571	0.749	0.791	0.823	0.815	
stand deviation +/-	0.013	0.002	0.013	0.024	0.021	0.012	0.018	0.019	0.018	0.023	
inhibition of stimulation in %	0.0	100.1	95.1	89.8	99.1	51.9	31.8	15.9	3.8	18.1	0.34

group	Compound III in μM											
	control	400	80	16	3.2	0.64	0.128	0.0256	0.00512	0.0010	0.0002	IC50 in μM
control	0.673	0.234	0.243	0.415	0.492	0.505	0.493	0.514	0.569	0.603	0.618	37.4
stand deviation +/-	0.013	0.043	0.008	0.007	0.012	0.007	0.004	0 019	0.018	0.007	0.016	
VEGF [10ng/m]	0.927	0.238	0.258	0.462	0.563	0.589	0.538	0.827	0.876	0.881	0.899	
stand devation +/-	0.034	0.032	0.005	0.007	0.017	0.014	0.009	0.008	0.031	0.029	0.014	
inhibition of stimulation %	0.0	98.3	90.2	81.3	76.2	74.7	42.9	-22.9	-20.9	-9.3	-10.6	0.28

group	Compound IV in μM											IC50 in μM
	control	400	80	16	3.2	0.64	0.128	0.0256	0.00512	0.0010	0.0002	
control	0.025	0.344	0.112	0.198	0.335	0.444	0.490	0.492	0.482	0.503	0.502	2.5
stand deviation +/-	0.018	0.024	0.004	0.008	0.012	0.017	0.018	0.006	0.013	0.012	0.008	
VEGF [10ng/m]	0.829	0.366	0.120	0.254	0.558	0.687	0.717	0.734	0.723	0.744	0.740	
stand devation +/-	0.009	0.014	0.012	0.007	0.014	0.012	0.014	0.013	0.016	0.013	0.014	
inhibition of stimulation %	0.0	89.5	96.2	72.3	-9.8	-19.2	-11.7	-19.3	-18.3	-18.3	-17.1	14.1

group	doxorubicin in μM											IC50 in μM
	control	400	80	16	3.2	0.64	0.128	0.0256	0.00512	0.0010	0.0002	
control	0.598	0.924	0.117	0.059	0.046	0.763	0.397	0.447	0.534	0.578	0.576	0.2
stand deviation +/-	0.025	0.052	0.002	0.003	0.003	0.008	0.013	0.017	0.021	0.015	0.024	
VEGF [10ng/m]	0.796	0.946	0.123	0.062	0.046	0.221	0.667	0.642	0.723	0.771	0.779	
stand devation +/-	0.017	0.071	0.001	0.004	0.002	0.015	0.006	0.010	0.007	0.011	0.006	
inhibition of stimulation %	0.0	88.6	96.8	98.2	100.3	70.5	19.0	1.3	4.3	2.7	-2.7	0.35

Table 2: Summary of IC_{50} determination of test substances on A10 cells without preincubation (without PDGF)

% control

substance	concentration in μM 0	400	80	16	3.2	0.64	0.128	0.0256	0.00512	IC50 in μM
Compd II	100	82	75	88	93	97	94	95	94	>400
Compd III	100	74	31	82	101	101	102	107	104	46.1
Compd IV	100	63	80	93	93	93	92	91	90	>400

Table 3: Summary of IC_{50} determination of reference and test substances on A10 cells with preincubation (without PDGF)

% control

substance	concentration in μM 0	400	80	16	3.2	0.64	0.128	0.0256	0.00512	IC50 in μM
Compd II	100	55	79	89	97	98	95	96	103	>400
Compd III	100	74	21	47	92	94	96	97	95	17.5
Compd IV	100	32	67	87	87	88	97	85	84	172

% control

substance	concentration in μM 0	100	20	4	0.8	0.16	0.032	0.0064	0.00128	0.000256	
doxorubicin	100	12	10	8	18	52	57	73	82	883	IC50 0.064 μM

Table 4: Summary of inhibition of PDGF-stimulation by test substances without preincubation extinction

substance	Compound II in μM 0	400	80	16	3.2	0.64	0.128	0.0256	0.00512	
control	0.645	0.388	0.485	0.568	0.601	0.628	0.606	0.611	0.607	
stand deviation +/-	0.010	0.041	0.014	0.007	0.013	0.012	0.012	0.007	0.007	
PDGF 0.1 μg/ml	1.245	0.642	0.539	0.677	1.103	1.256	1.129	1.131	1.116	
stand deviation +/-	0.028	0.141	0.012	0.018	0.048	0.038	0.020	0.025	0.029	
inhibition of stimulation in %	0.0	59.3	91.0	82.0	16.2	-4.7	12.8	13.3	15.2	IC50 7.5 μM

substance	Compoun III in μM 0	400	80	16	3.2	0.64	0.128	0.0256	0.00512	
control	0.694	0.514	0.216	0.572	0.699	0.700	0.706	0.741	0.722	
stand deviation +/-	0.029	0.032	0.012	0.034	0.044	0.020	0.031	0.026	0.038	
PDGF 0.1 μg/ml	1.150	0.485	0.143	0.902	1.079	1.068	1.090	1.083	1.105	
stand deviation +/-	0.011	0.027	0.010	0.010	0.030	0.017	0.017	0.012	0.008	
inhibition of stimulation in %	0.0	106.4	116.0	27.5	16.7	19.2	15.8	24.9	16.0	IC50 20.1 μM

substance	Compound IV in μM 0	400	80	16	3.2	0.64	0.128	0.0256	0.00512	
control	0.698	0.442	0.559	0.650	0.650	0.647	0.640	0.634	0.627	
stand deviation +/-	0.034	0.020	0.019	0.025	0.021	0.028	0.018	0.015	0.016	
PDGF 0.1 μg/ml	1.208	0.500	0.726	0.888	0.892	1.052	1.184	1.208	1.128	
stand deviation +/-	0.036	0.044	0.022	0.026	0.025	0.054	0.050	0.040	0.037	
inhibition of stimulation in %	0.0	88.8	67.2	53.4	52.5	20.7	-6.7	-12.4	1.8	IC50 7.4 μM

Table 5: Summary of inhibition of PDGF-stimulation by reference and test substances with preincubation

substance	Compound II in μM 0	400	80	16	3.2	0.64	0.128	0.0256	0.00512	
control	0.875	0.484	0.691	0.781	0.852	0.855	0.834	0.857	0.905	
stand deviation +/-	0.048	0.037	0.042	0.037	0.053	0.038	0.041	0.058	0.075	
PDGF 0.1 μg/ml	1.587	0.597	0.792	0.854	1.279	1.581	1.528	1.590	1.573	
stand deviation +/-	0.076	0.078	0.075	0.065	0.060	0.079	0.065	0.086	0.088	
inhibition of stimulation in %	0.0	84.2	85.8	75.7	40.1	-2.1	2.4	-3.0	6.1	IC50 4.6 μM

substance	Compound III in μM 0	400	80	16	3.2	0.64	0.128	0.0256	0.00512	
control	0.777	0.575	0.162	0.382	0.713	0.728	0.746	0.754	0.741	
stand deviation +/-	0.010	0.055	0.009	0.008	0.005	0.013	0.015	0.015	0.010	
PDGF 0.1 μg/ml	1.452	0.613	0.211	0.736	1.355	1.382	1.390	1.401	1.403	
stand deviation +/-	0.030	0.027	0.025	0.067	0.010	0.014	0.009	0.014	0.018	
inhibition of stimulation in %	0.0	94.3	92.9	44.6	5.0	3.1	4.7	4.1	2.0	IC50 18.2 μM

substance	Compound IV in μM 0	400	80	16	3.2	0.64	0.128	0.0256	0.00512	
control	0.763	0.241	0.513	0.666	0.663	0.572	0.663	0.658	0.640	
stand deviation +/-	0.054	0.028	0.020	0.017	0.023	0.015	0.015	0.040	0.012	
PDGF 0.1 μg/ml	1.384	0.298	0.696	0.802	0.824	0.942	1.209	1.333	1.334	
stand deviation +/-	0.028	0.025	0.022	0.031	0.018	0.044	0.030	0.041	0.025	
inhibition of stimulation in %	0.0	90.8	70.6	78.2	74.1	56.5	12.0	-8.8	-11.8	IC50 0.97 μM

extinction

substance	Doxorubicin in μM 0	100	20	4	0.8	0.16	0.032	0.0064	0.00128	0.000256	
control	0.635	0.078	0.063	0.052	0.116	0.331	0.359	0.461	0.520	0.557	
stand deviation +/-	0.021	0.009	0.012	0.011	0.009	0.007	0.006	0.007	0.011	0.019	
PDGF 0.1 μg/ml	1.467	0.094	0.071	0.065	0.289	0.609	0.653	0.934	1.164	1.296	
stand deviation +/-	0.009	0.011	0.010	0.009	0.016	0.017	0.007	0.013	0.011	0.038	
inhibition of stimulation in %	0.0	98.0	99.1	98.5	79.3	66.6	64.6	43.2	22.7	11.1	IC50 0.016

Table 6: Summary of effects of test compounds in the adjuvant arthritis rat model compared to arthritis control + vehicle (772-22)

					Drug Treatment:	
Adjuvant Arthritis		Test No: 186	% Change Day 18		Day: 1-18 i.p.	
No	Compound	Dose mg/kg	Paw Volume 1)	Weight 2)	Index 1)	
1	Healthy Control			21		
2	Arthritis Control		37	10	44	(untreated)
3	Arthritis Control +	Vehicle		13		(5 ml/kg)
4	Compound II	8	17	12	20	--
5	Compound II	16	-28	17	-35	--
6	Compound III	8	-59	25	-79	--
7	Compound III	16	-33	16	-39	--
8	Compound IV	8	-44	15	-61	(10 ml/kg)
9	Compound IV	16	-57	16	-64	--

1) Compared to Arthritis - Control (Vehicle)
2) Bodyweight gain compared to day one

Table 7: Summary of effects of test compounds on the index in adjuvant arthritis rats compared to arthritis control + vehicle (772-22)

Adjuvant Arthritis			Index
	Test No.: 186		Day: 18
	Index	Δ %	
Arthritis Control	37.75	44	
Arthritis Control + 772-22	26.3		
Compound II, 8 mg/kg i.p.	31.5	20	
Compound II, 16 mg/kg i.p.	17.0	-35	
Compound III, 8 mg/kg i.p.	5.5	-79	
Compound III, 16 mg/kg i.p.	16.0	-39	
Compound IV, 8 mg/kg i.p.	10.2	-61	
Compound IV, 16 mg/kg i.p.	9.5	-64	